

PATENT
Attorney Docket No. PC10770B US

REMARKS

I. Status

Claims 10, 11, and 20-33 are pending in the application. Claims 10-11, 20, and 22-33 are currently amended to reflect the present election. Claim 21 is currently withdrawn, as discussed in greater detail below.

The disclosure is objected to for certain informalities. The abstract is additionally objected to.

Claims 10-11, 20, 22-33 stand rejected under 35 U.S.C. § 112, ¶2 with regard to in part certain claim terms. Claims 10-11, 20, and 22-33 stand rejected under 35 U.S.C. § 112, ¶1 for enablement. Claims 10, 11, 20, and 33 stand rejected under 35 U.S.C. § 103(a) over WO 98/56771 ("Bauman"). Claims 10, 11, 20, 25, and 26 stand rejected under the obviousness-type double patenting doctrine over the parent to the present application, U.S. Pat. No. 6,649,611. Applicants traverse each of the rejections.

II. Restriction Requirement

Applicants are being required to elect one of the following groups pursuant to 35 U.S.C.

§ 121:

- I. Claims 10, 11, 20, 22-33, drawn to compounds and compositions where R^4 =aryl, classified in class 544, subclasses such as 391, 357, 121 and many others.
- II. Claims 10, 11, 20, 22-23, drawn to compounds, compositions, where R^4 =heteroaryl, classified in class 544, subclasses such as 238 when pyridazine is R^4 , 235 when cinnoline is R^4 , 363 when R^4 =quinoline and many others.

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- III. Claims 10, 11, 21-33, drawn to compounds, compositions, where R^4 =aryl, classified in class 544, subclasses such as 391 and others.
- IV. Claims 10, 11, 21-33, drawn to compounds, compositions where R^4 =heteroaryl, classified in class 544, subclasses various based on the exact nature of species exemplified.

Applicants respectfully traverse the restriction requirement. MPEP § 803 states that the two criteria for a proper requirement for restriction are (1) the inventions must be independent or distinct as claimed, and (2) there must be a serious burden on the Examiner if restriction is required. Here, the Examiner has not shown that there would be a serious burden on the Examiner if restriction were not required. Rather, the Examiner states at page 3 of the Office Action, "Each [group?] can support a patent as the compounds are made and used independently of each other." But, the Examiner has not indicated with specificity how a search for the compounds and compositions defined by the claims as previously presented would present a serious burden on the Examiner.

Nevertheless, to advance the prosecution of the present application and to be fully responsive to the present restriction requirement, Applicants elect Group I (Claims 10, 11, 20, 22-33) with traverse for examination purposes. In that regard, non-elected claim 21 is withdrawn without prejudice to pursuing the subject matter of such claim in any continuing application, such as, e.g., a continuation application, a divisional application, etc.

In addition, the Examiner is requiring Applicants to elect a single species. In response, Applicants elect the species of example 23.

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III. Miscellaneous Objections to the Application

The disclosure is objected to for certain informalities. In particular, the Examiner asserts that the parent history needs complete revision. Applicants understand this comment to be limited to the Examiner's request to update the status of the parent application listed in the priority claims. Applicants believe the foregoing amendment to the priority claim addresses the Examiner's objection. To the extent clarification is required, the Examiner is urged to telephonically contact the undersigned.

In addition, the abstract is objected to because the Examiner asserts that none of the variables "are as defined above" but rather as defined in the specification. An error of a grammatical error is also indicated. Applicants believe the objection to the Abstract is overcome in view of the foregoing amendment. As such, removal of the present objections to the specification is respectfully requested at this time.

IV. Claims 10-11, 20, 22-33 are Definite

Claims 10-11, 20, 22-33 stand rejected under § 112, ¶2 with regard to in part certain claim terms. Applicants respectfully traverse the rejection.

First, the Examiner asserts that the scope of the term "acetyl" is indefinite because as used in the definition of R⁵ in the relevant claims and possibly in the specification, the term is defined in the specification to supposedly mean something that is not art-recognized. Applicants respectfully disagree with the Examiner's assertion because the specification clearly defines the term "alkyl" in an art-recognized manner at page 18, lines 1-2: "The term 'acetyl', as used herein, refers to an

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'alkyl-carbonyl' moiety wherein alkyl is defined as above." Thus, the term "acetyl" is not limited to mean $C(O)CH_3$ as the Examiner suggests.

The Examiner further asserts at page 2 of the Office Action that if the term "acetyl" is intended to have the broader meaning $C(O)$ alkyl, then the "special" definition for the term "acetyl" needs to be recited in the main claim. Applicants believe that the term "acetyl" need not be recited in the claim because the suggested amendment is inappropriate.

The Examiner is respectfully reminded that it is not uncommon for claim terms to be defined in the specification because the exact meaning of the term need not be defined in the claim. The fact that a claim term can be defined without an explicit definition in the specification does not make it inappropriate to define such a claim term in the specification. "[T]he definiteness of the language employed must be analyzed - not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 439 F.2d 1232, 1235 (CCPA 1971). "It is important here to understand that under this analysis claims which on first reading - in a vacuum, if you will - appear indefinite may upon a reading of the specification disclosure or prior art teachings become quite definite." *Id.* Certainly, those of skill in the art, e.g., chemical practitioners, viewing the relevant claims in a vacuum would know to consult the specification for any "special" definitions of claim terms because of the many different meanings available for even fundamental claim terms. Here, Applicants have provided such a definition (cited above) leaving no doubt to those of skill in the art as to the meaning of the term "alkyl".

Moreover, amending the relevant claims in accordance with the Examiner's suggestion could possibly render *other* claim terms having "special" meanings indefinite. In such a case, it

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would be anticipated that such other claim terms would require an amendment similar to that presented suggested by the Examiner. In effect then, the Examiner appears to suggest that every claim term that has a "special" meaning be defined in the claim. Thus, the presently suggested amendment would create a windfall in which the Federal Circuit may have sought to prevent.

Second, the Examiner asserts that the claim terms "heterocycloalkyl" and "heteroaryl" are indefinite because the definition for each term in the specification is non-limiting (citing the word "etc."). Applicants believe the cited claim terms are definite in view of the foregoing amendments to the specification.

Third, the Examiner indicates that claim 33 contains improper punctuation. Claim 33 as amended is now believed to contain proper punctuation.

Fourth, the Examiner requests that the superfluous phrases of "wherein R⁵ is" be removed from claim 20. Applicants have amended claim 20 accordingly.

Fifth, the Examiner asserts that claims 10 and 11 are substantial duplicates because the Examiner is not giving the preambles of the cited claims material weight. Applicants respectfully traverse the rejection because material weight should be given to the preambles of each of claims 10 and 11. It is well settled that "a preamble limits the invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) citing *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305. (emphasis added). Here, it is clear that the preamble of each of claims 10 and 11 gives "life and meaning" to the claims since the body of each claim explicitly references "such disorder or condition." Claims 10 and 11 would not make sense if the preamble of each claim were not considered since the body of each claim specifically references the diseases or

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conditions listed in the preamble.

The Examiner's citation of *In re Tuominen* is not relevant to the present application as the cited case concerns the weight given to preambles in view of a prior art rejection. *In re Tuominen*, 671 F.2d. 1359 (CCPA 1982). Here, there is no such prior art rejection.

For at least the forgoing reasons, removal of the present rejection is respectfully requested at this time.

V. Claims 10-11, 20, 22-33 are Enabled

Claims 10-11, 20, and 22-33 stand rejected under § 112, ¶1 as lacking enablement. Applicants respectfully traverse this rejection.

In particular, the Examiner asserts at page 6 of the Office Action that the specification does not enable those of skill in the art to make and use the scope of elected piperazines claimed, especially with respect to variable R⁵. The present disclosure does enable those of skill in the art to make and use the scope of piperazines claimed. As stated in Applicants' Response dated January 28, 2003 for parent application USSN 09/821,322, an example need not be provided for each species. A skilled worker would expect that the examples and schemes 1-2 could be modified, if necessary, to make compounds with various R⁵ substituents in the same manner without undue experimentation. For example, scheme 1 reaction 2 is a demonstration of making compounds of formula I using compounds of formula H-(Z)_e-R⁴ wherein e is 1 and Z is oxygen. A skilled worker would expect such a reaction to be operative for all R⁵ substituted derivatives. The Examiner does not appear to deny this point as indicated in a subsequent Office Action dated April 4, 2003.

Rather, the Examiner appears concerned that those of skill in the art would not be enabled to

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use the scope of piperazines claimed. Applicants fail to see, however, how those of skill in the art would *not* be able to use the claimed piperazine compounds. At page 1 of the specification, Applicants plainly disclose, "The compounds of the present invention are potent and selective inhibitors of chemokine binding to its receptor CCR1 found on inflammatory and immunomodulatory cells (preferably leukocytes and lymphocytes). . ." At pages 39-41 of the specification, Applicants describe in detail the pharmacological properties and the relevant Chemotaxis Assay for the claimed compounds. Further, Applicants even disclose at page 41 the potency of the compounds as being less than 25 μ M in the Chemotaxis assay. In view of the ample disclosure provided by Applicants, those of skill in the art would be able to use the claimed piperazine compounds.

With regard to the *In re Wands* factors cited by the Examiner, Applicants note that the Examiner only analyzes four of the eight factors, which is improper. For instance, the Examiner did not analyze the level of ordinary skill in the art. Applicants respectfully remind the Examiner that here, the level of ordinary skill in the art is high. Consequently, Applicants need not provide every particular concerning the use of the compounds as such information is readily within the scope of knowledge of those of skill in the art. Of course, other factors weigh in favor of Applicants, which are not detailed here solely for the sake of brevity.

In view of the foregoing remarks, removal of the present rejection is respectfully requested at this time.

VI. Claims 10, 11, 20, and 33 are Patentable Over Bauman

Claims 10, 11, 20, and 33 stand rejected under § 103(a) over Bauman. Applicants

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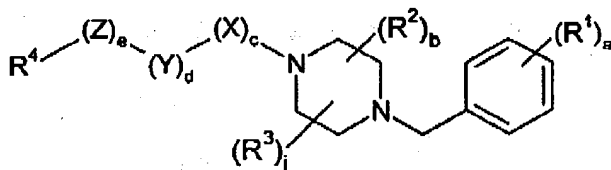
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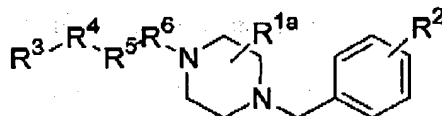
respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the reference(s) must teach or suggest all of the claim elements. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Third, there must be a reasonable expectation of success. Here, Applicants believe that Bauman fails to satisfy all three of the basic criteria.

Present claim 20 defines compounds of formula I:



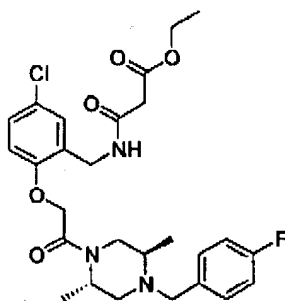
R⁴ is defined as being (R⁵)_f(R⁶)_g(C₆-C₁₀)aryl. Bauman, on the other hand, discloses compounds of the formula:



Bauman discloses R³ as being a carbocyclic ring system substituted by one or more independently selected substituents corresponding in placement to R⁵ and R⁶ of present claim 20.

First, Bauman fails to teach or suggest each and every element defined by claim 20. The Examiner cites the Bauman compound at page 52, line 26, (trans)-1-((4-chloro-2-((ethoxycarbonylmethylcarbonyl)aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-

fluorobenzyl)piperazine, as being an obvious variant of the scope of claim 20. The cited compound has the structure below:



As seen immediately above, the chloro group corresponds with Applicants' R^6 (and not R^5) because R^6 is defined in part as being halo; R^5 is not defined as being chloro. As such, the alkoxycarbonylalkylcarbonylaminoalkyl substituent would have to correspond to Applicants' R^5 in order for the Bauman compound to be within the scope of the present claims. But, claim 20 does not define R^5 as being alkoxycarbonylalkylcarbonylaminoalkyl. At best, R^5 is defined in part as being (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkylamino(C₁-C₆)alkyl. When noting this difference, the Examiner indicates that the Bauman substituent differs "only in having a carbonyl group present in the complex moiety present on the phenyl ring." As such, the Examiner appears to trivialize the difference between the Bauman substituent and the cited R^5 substituent and determine that the difference is obvious.

Applicants contend, however, that the difference between the Bauman substituent and the present R^5 substituent is not obvious because the difference in substituent results in two different structures. As a result of having the additional carbonyl, the Bauman compound has an amide bond proximal to the chloro-substituted phenyl ring. In contrast, because the cited R^5 substituent does not have the "additional" carbonyl, the resulting structure has a secondary amine proximal to the chloro-

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substituted phenyl ring. To conclude that the Bauman compound renders claim 20 obvious would essentially require one to determine that an amide would render a secondary amine obvious.

Further, those of skill in the art appreciate the potentially significant differences between an amide and a secondary amine. Noting just one example, an amide and a secondary amine would presumably have different pharmacological activities because of, e.g., their different geometries. Of course, those of skill in the art will readily appreciate other differences. Further, the Examiner has not indicated *with support* how the cited functional group difference would establish obviousness. Thus, Bauman does not teach or suggest each and every element defined by claim 20. As such, claim 20 is patentable over Bauman for this independent, patentably distinct reason.

Second, Bauman does not teach or suggest a modification to arrive at the compounds defined by claim 20. In particular, Bauman does not teach or suggest a modification to arrive at Applicants' R⁵ substituents. For example, Bauman teaches at page 61, line 21-25 that the most preferred compounds are those having R³ as phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido. The substituents at the 4-position must correspond to Applicants' R⁶ since, as mentioned above, R⁵ is not defined as being chloro. Consequently, the substituent at the 2-position would have to correspond with Applicants' R⁵. But, the preferred substituents taught by Bauman at the 2-position (aminocarbonyl, ureido, and glycinamido) do not correspond with Applicants' R⁵. As such, a modification of Bauman's most preferred teachings would not arrive at Applicants' claimed compounds.

Indeed, Bauman does not indicate which of the six variables (R^{1a}, R², R³, R⁴, R⁵, R⁶ and variables within some of these R groups) is a critical variable. At best, Bauman teaches a number of preferred choices for R^{1a}, R², and substituents on a phenyl R³ group within the class of compounds

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when R^4 is $-O-$, R^5 is methylene, and R^6 is $-C(O)-$. Bauman, however, does not point to any one variable as more critical than the others. In that regard, Bauman does not teach or suggest removing the "additional" carbonyl from the substituent of the compound at page 52, line 26 to arrive at the present R^5 substituent. This lack of teaching of critical parameters would not motivate those of skill in the art to modify the Bauman compounds to arrive at the presently claimed compounds.

Third, absent such a teaching or motivation in Bauman as discussed above, there is no reasonable expectation of success. Given the considerable number of variables that may be modified, without motivation, those of skill in the art would have to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result. As such, the Examiner is apparently basing this rejection on an "obvious to try" rationale, which is impermissible.

In view of the foregoing remarks, Applicants respectfully request removal of this rejection at this time.

VII. Claims 10, 11, 20, 25, and 26 are Patentable Over U.S. 6,649,611

Claims 10, 11, 20, 25, and 26 stand rejected under the obviousness-type double patenting doctrine over the parent application, which issued as U.S. Pat. No. 6,649,611. Applicants are submitting herewith a terminal disclaimer, which, as the Examiner indicates at page 10 of the Office Action, can be used to overcome an obviousness-type double patenting rejection. As such, the present rejection is overcome.

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VIII. Conclusion

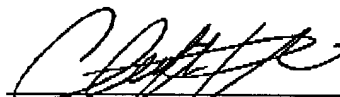
Having addressed all outstanding issues, Applicants kindly request removal of all rejections and allowance of all pending claims at this time. To the extent the Examiner believes that it would facilitate allowance of this case, the Examiner is urged to call the undersigned at the number below.

Applicants believe that no fee is associated with the filing of this paper, as it is being filed within the three-month Shortened Statutory Period, i.e., the next business day after three months from the date of the Examiner's Office Action. However, to the extent a fee is due, the Commissioner is hereby authorized by this paper to charge any required fees or credit any overpayment to Deposit Account 16-1445.

Respectfully submitted,

Date:

September 27, 2004



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